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FILING DATE: *May 26, 2004*

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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

Express Mail Label No. EV332143975US

INVENTOR(S)

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☐ *Additional inventors are being named on the_____ separately numbered sheets attached hereto*

TITLE OF THE INVENTION (500 characters max)

Direct all correspondence to: **CORRESPONDENCE ADDRESS**

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ENCLOSED APPLICATION PARTS *(check all that apply)*

☒ Specification *Number of Pages*	22	☐ CD(s), Number	
☒ Drawing(s) *Number of Sheets*	1	☐ Other (specify)	
☐ Application Data Sheet. See 37 CFR 1.76			

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Respectfully submitted,

SIGNATURE Robert J. Smith

Date 05/26/2004

TYPED or PRINTED NAME Robert J. Smith

REGISTRATION NO. *(if appropriate)* 40,820

Docket Number: PB60817P1

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CERTIFICATE OF MAILING BY "EXPRESS MAIL" (37 CFR 1.10) Applicant(s): **SHAPLAND, Penberthy David Peter, et. al.**			Docket No. **PB60817P1**
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Invention: **CHEMICAL PROCESS**

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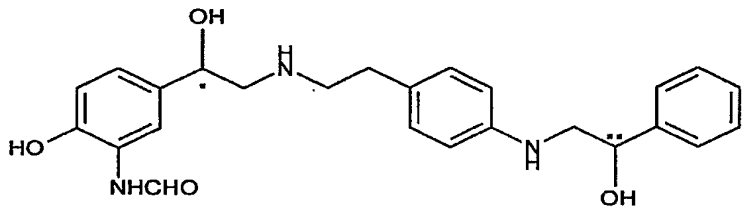
CHEMICAL PROCESS

The present invention relates to the preparation of a β_2 adrenergic agonist in crystalline salt form. In particular the invention relates to preparation of a crystalline salt of compound (I) defined below. More particularly the invention relates to a process for preparing a crystalline monohydrochloride salt of compound (Ia) defined below.

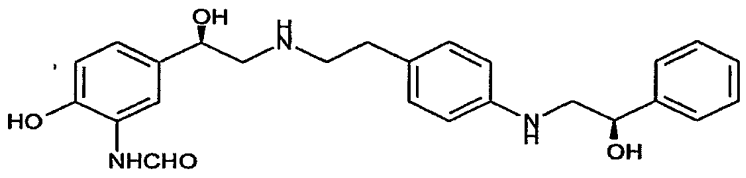
β_2 Adrenergic receptor agonists are recognized as effective drugs for the treatment of pulmonary diseases such as asthma and chronic obstructive pulmonary disease (including chronic bronchitis and emphysema). β_2 Adrenergic receptor agonists are also useful for treating premature labour, and are potentially useful for treating neurological disorders and cardiac disorders.

International Patent Application WO 01/42193 and corresponding US Patent No. 6,576,793 disclose *inter alia* a novel compound of the formula (I):



(I)

wherein the stereochemistry at *C and **C may be *inter alia* (R) and (R). This compound may be more particularly represented by the formula (Ia):



(Ia)

Compound (Ia) may variously be referred to by the chemical names *N*-{2-[4-((*R*)-2-hydroxy-2-phenylethylamino)phenyl]ethyl}-(*R*)-2-hydroxy-2-(3-formamido-4-hydroxyphenyl)ethylamine; *N*-[3-[(1*R*)-1-hydroxy-2-[[2-[4-[(2*R*)-2-hydroxy-2-phenylethyl)amino]phenyl]ethyl]amino]ethyl-6-hydroxyphenyl]-formamide and *(α-R)*-3-

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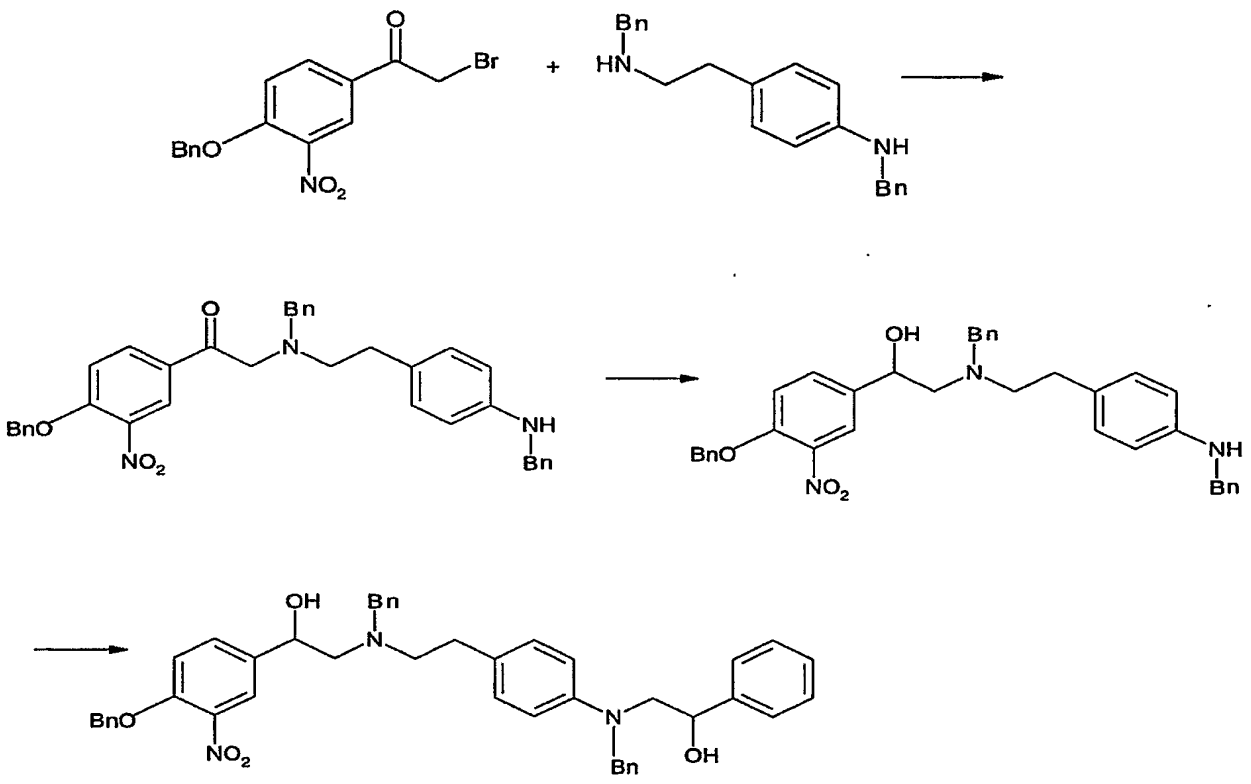
formamido-4-hydroxy-(α-[[[p-(N-((2*R*)-hydroxy-phenethyl))-amino-phenethyl]amino]methyl benzyl alcohol. In CAS format the compound (Ia) is designated:

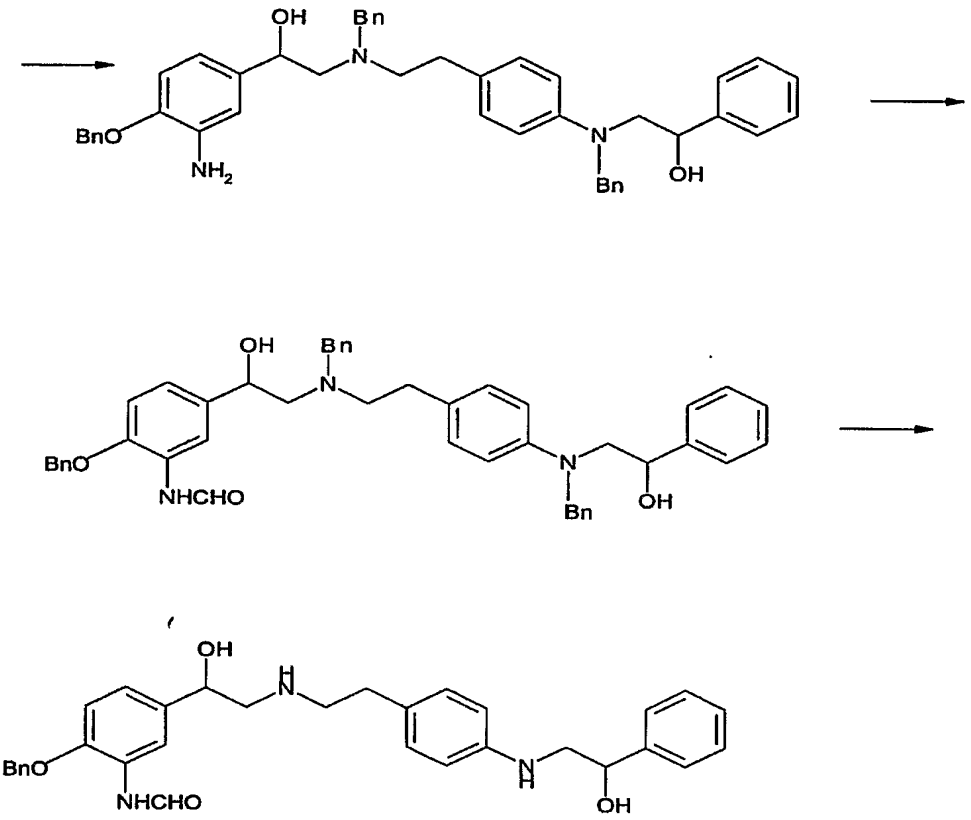
N-[2-hydroxy-5-[(1R)-1-hydroxy-2-[[2-4-[[(2R)-2-hydroxy-2-phenylethyl]amino] phenyl]ethyl]amino]ethyl]phenyl]-formamide.

Compound (Ia) is a potent β_2 adrenergic receptor agonist.

WO 01/42193 and US Patent No. 6,576,793 describe the preparation of compound (Ia) as a mixture of stereoisomers, that is, wherein the stereochemistry at *C is (RS) and the stereochemistry at **C is (RS), according to the following reaction scheme:

Scheme 1

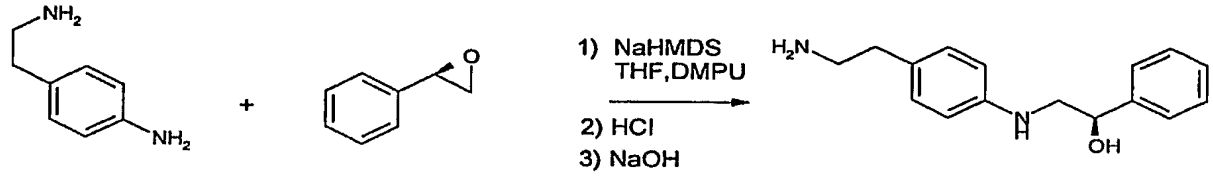




wherein Bn represents a benzyl protecting group.

US patent application no 10/627,555 and corresponding International published application WO 04/011416 describe the crystalline dihydrochloride salt of compound (Ia) and methods for preparing said salt. In said applications, compound (Ia) is prepared according to the following reaction scheme 2:

Scheme 2



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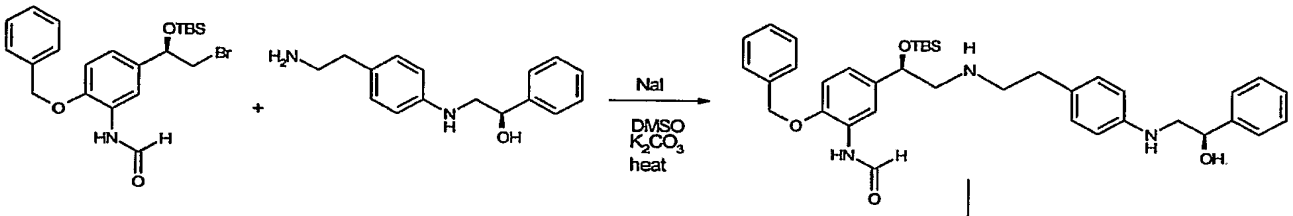
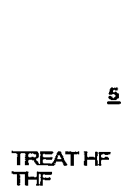
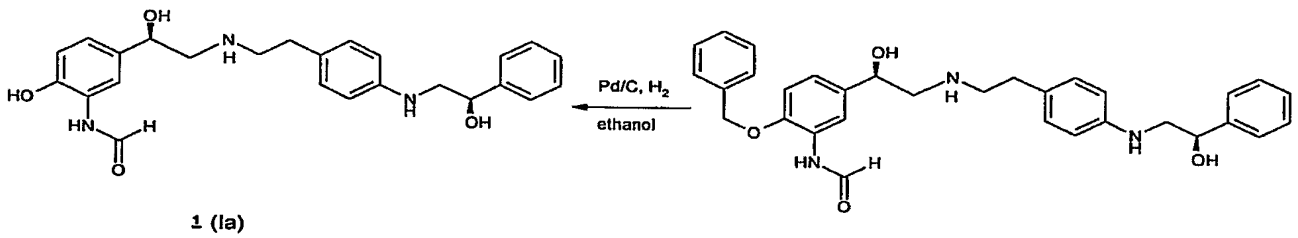
3 4

5



4 2 5





1 (Ia) 6

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In Scheme 2 the abbreviations used have the following meanings:

NaHMDS:	sodium hexamethyldisilazane
THF:	tetrahydrofuran
DMPU:	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)pyrimidinone
TBDMSCl:	tert-butyldimethylsilylchloride
DMF:	dimethylformamide
DMSO:	dimethylsulphoxide
TREAT HF:	triethylamine trihydrofluoride

The numbering of compounds in Scheme 2 follows that in WO 04/011416, but it will be appreciated that compound **1** in Scheme 2 is equivalent to compound (Ia) herein.

According to WO 04/011416, the dihydrochloride salt of compound **1** is prepared by dissolving compound **1** in a polar solvent to form a first solution and adding hydrochloric acid to form a second solution from which the dihydrochloride salt is formed by crystallisation.

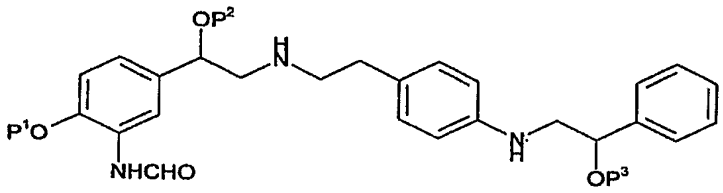
We have now found a method for preparing a monohydrochloride salt of compound (I), in particular a monohydrochloride salt of compound (Ia) and most preferably a crystalline monohydrochloride salt of compound (Ia).

It will be appreciated from the foregoing that the compound of formula (I) includes two asymmetric centres, namely at the carbon atoms designated in formula (I) as *C and **C. References herein to compounds of formula (I) include both (*S*) and (*R*) enantiomers either in substantially pure form or admixed in any proportions, at both *C and **C. Thus, the stereochemistry at *C and **C may be (*RS*) and (*RS*), (*R*) and (*R*), (*R*) and (*S*), (*S*) and (*R*), or (*S*) and (*S*).

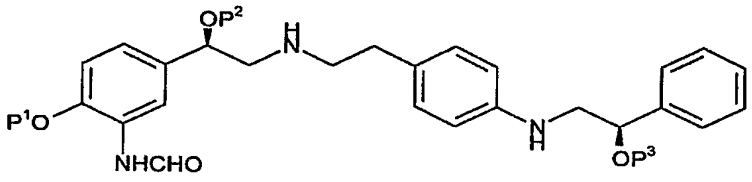
Hereinafter references to compound (I) should be read as including in particular compound (Ia) unless otherwise specified.

Thus, in a first aspect the present invention provides a process for preparing a monohydrochloride salt of compound (I) which process comprises the steps of:

a) contacting a protected form of compound (I), or compound (Ia) (hereinafter compound (II) and (IIa) respectively):



(II)



(IIa)

wherein P^1 represents a hydroxyl protecting group, such as benzyl, and P^2 and P^3 each independently represent hydrogen or a hydroxyl protecting group;

with a weak acid, eg. acetic acid, to effect selective protonation;

b) contacting the product of (a) with a source of chloride ions eg. sodium chloride, to effect anion exchange;

c) deprotecting the product of (b) to remove P^1, and where necessary P^2 and P^3;

d) isolation of compound (I) or (Ia) as a monohydrochloride salt; and optionally

e) crystallisation or recrystallisation of compound (I) or (Ia).

Examples of the hydroxyl protecting group P^1 include arylalkyl eg. benzyl. Where either or both of P^2 and P^3 represent protecting groups these may be groups which can be selectively removed under conditions which do not also remove P^1. Thus, each of P^2 and P^3 may be for example a silyl group, eg. a trialkyl silyl group such as tert-butyldimethyl

silyl. In one embodiment of this invention P^1 represents a protecting group and P^2 and P^3 both represent hydrogen.

It will be appreciated by those skilled in the art that compounds (I) and (Ia) contain two basic nitrogen atoms and thus have the potential to from salts at both. In order to obtain a monohydrochloride directly, ie. by reaction of compound (II) or (IIa) with hydrochloric acid, the reaction must be carefully controlled to achieve the correct stoichiometry, and avoid formation of eg. a dihydrochloride salt.

We have found that effecting initial protonation with a weak acid such as acetic acid results in selective protonation of only one nitrogen atom (the more basic nitrogen atom) and, following anion exchange, formation of a stoichiometrically exact monohydrochloride salt. The process of the present invention also has the advantage that the hydrochloride salt can be prepared without the use of strong acid. It is desirable to avoid the use of a strong acid as this can lead to deformylation of the parent compound.

In step (a) of the present process, a compound of formula (II) or (IIa), conveniently in an organic solvent such as 2-butanone (methylethylketone), or diethylketone may be contacted with a weak acid. Weak acids which may be employed include for example acetic acid, 2-methoxybenzoic acid or 4-methoxybenzoic acid. This may conveniently be effected at a slightly elevated temperature, for example at a temperature in the range from about 25°C to about 50°C.

Step (b) may conveniently be effected without isolating the product from step (a). Thus for example the solution obtained from step (a) may be contacted with a source of chloride ions, using eg. aqueous sodium chloride. This step may also conveniently be effected at a temperature in the range from about 25°C to about 50°C. At this stage the intermediate product may be isolated using conventional methods to provide the monohydrochloride salt of compound (II) or (IIa). This product may be obtained in crystalline form.

Deprotection of (II) or (IIa) according to step (c) may be effected by conventional methods. Thus where one or both of P^2 and P^3 represents a silyl group this may be removed for example using cesium fluoride, in an organic solvent such as methanol, optionally in admixture with a further solvent such as diethylketone, methylethylketone or n-butylacetate, or triethylamine trifluoride in a solvent such as tetrahydrofuran. A protecting

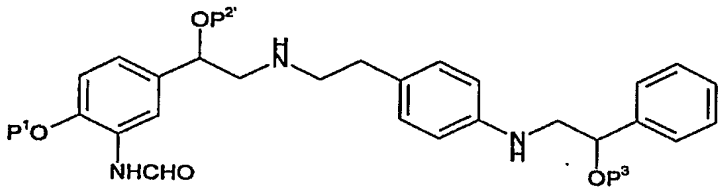
group P^1 may be removed for example by hydrogenation using a palladium or platinum catalyst eg. Pd/C, conveniently in an organic solvent such as N-methylpyrrolidone.

Monohydrochloride salt of compound (I) or (Ia) prepared according to the present invention may be isolated by conventional means. Advantageously said monohydrochloride salt of compound (Ia) may be obtained in crystalline form, by precipitation from an aqueous organic solution. In a particular embodiment crystalline (Ia) monohydrochloride may be obtained from an organic solution comprising a mixture of N-methylpyrrolidone and isopropylalcohol (preferably 1:1), by heating said solution to a temperature in the range from about 60°C to about 80°C, adding water and then contacting the resulting aqueous solution with further isopropylalcohol. During addition of further isopropyl alcohol the temperature is cooled, initially in the range from about 15°C to about 25°C and subsequently in the range from about 0° to about 10°.

Recrystallisation of monohydrochloride salt of compound (I) or (Ia) may be effected by suspending or dissolving said compound in a suitable solvent, for example industrial methylated spirits, optionally in admixture with water, and initiating crystallisation in conventional manner, eg. with cooling.

The present invention also provides crystalline (Ia) monohydrochloride (alternatively crystalline *N*-{2-[4-*((R)*-2-hydroxy-2-phenylethylamino)phenyl]ethyl}-(*R*)-2-hydroxy-2-(3-formamido-4-hydroxyphenyl) ethylamine monohydrochloride) in a form which is characterised by a differential scanning calorimetry trace which shows an absence of discernable endothermic features below about 125°C, two or more minor endothermic events between about 130 °C and about 180 °C and an onset of significant endothermic heat flow at about 229°C. For example, said minor endothermic events may occur at about 133 °C and at about 151 °C; in addition a further minor endothermic event may occur at about 170 °C.

The compound of formula (II) or (IIa) wherein P^2 and P^3 both represent hydrogen may be obtained from a corresponding compound of formula (III).



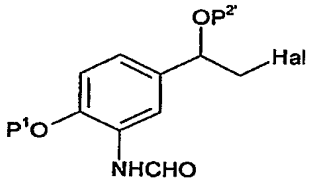
(III)

wherein P^1 and P^3 are as defined for compound (II) and $P^{2'}$ is a hydroxyl protecting group. $P^{2'}$ may be selected from hydroxyl protecting groups known in the art, e.g. a silyl group such as tert-butyldimethylsilyl. It will be appreciated that P^1, $P^{2'}$ and P^3 should be selected such that $P^{2'}$ and P^3 can be removed under conditions which will not also remove P^1.

When $P^{2'}$ represents a tert-butyldimethylsilyl group this may conveniently be removed using cesium fluoride, in an organic solvent such as methanol, optionally in admixture with a further solvent such as diethylketone, methylethylketone or n-butylacetate.

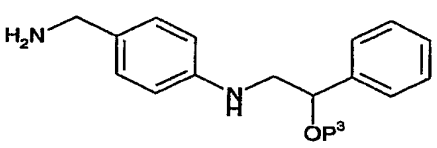
It will be understood that when it is desired to obtain a compound (Ia) the appropriate chiral intermediate is desirably employed in this stage and in the stages described hereinafter. Structures (III) (IV) and (V) should therefore be interpreted as depicting the individual chiral forms as well as mixtures thereof.

A compound (III) may be obtained by reaction of a compound (IV):



(IV)

wherein Hal is a halo leaving group, eg. bromo, and $P^{2'}$ is as defined for formula (III) with a compound (V):



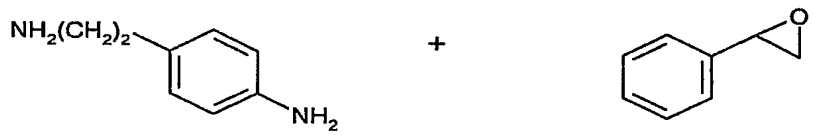
(V)

wherein P^3 is as defined for formula (III).

The reaction of (IV) and (V) may conveniently be effected in the presence of a base, such as potassium carbonate and in a solvent such as N,N-dimethylacetamide.

Compounds (IV) and (V) may be coupled, in a solvent such as N,N-dimethylacetamide or dimethylsulphoxide, by adding potassium carbonate and sodium hydroxide or sodium iodide and heating to a temperature in the range of about 90°C to about 140°C to form a compound (III), which may be further reacted without isolation.

The compound (V) may be obtained by coupling 2-(4-aminophenyl)ethylamine and styrene oxide.



It will be appreciated that to prepare a compound (Ia), the correct chiral form of compound (V) should be employed. This may be prepared by employing (R)-styrene oxide in the above reaction.

The amine, which is optionally provided as a salt, may first be reacted with between about 1 and about 1.2 equivalents of a base having a pK_a value greater than about 18, in order to substantially deprotonate the 4-amino group. The (R)-styrene oxide is added to the product of the amine reaction. Useful basic compounds include sodium bis(trimethylsilyl)amide, alternatively known as sodium hexamethyldisilazane (NaHMDS), lithium diisopropyl amide, and n-butyl lithium. The reaction is preferably conducted in a solvent system including a polar aprotic solvent, such as 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)pyrimidinone (DMPU). Additional examples of aprotic polar solvents include dimethylsulfoxide, N-methyl pyrrolidinone, N;N-dimethyl acetamide, tetramethylethylenediamine, and hexamethylphosphoramide. After aqueous extraction, the product of the coupling reaction may be crystallized as the hydrochloride salt from a solvent such as isopropanol, by the addition of aqueous hydrochloric acid. The crystallization procedure efficiently separates the desired product from side products

formed during the reaction. The hydrochloride salt may be redissolved with 10 N aqueous sodium hydroxide to provide 2-[4-((R)-2-hydroxy-2-phenylethylamino) phenyl]ethylamine (compound (V)).

The corresponding (S) stereoisomer, 2-[4-((S)-2-hydroxy-2-phenylethylamino)phenyl] ethylamine, can be prepared by substituting (S)-styrene oxide for (R)-styrene oxide in the above procedure for the synthesis of compound (V).

Compounds of formula (IV) may be prepared by methods known in the art. Thus for example a compound of formula (IV) wherein P^2 is hydrogen may be prepared as described in US Patent No. 6,268,533 B1; and in R. Hett et al., Organic Process Research and Development, **1998,** 2, 96-99, or using procedures similar to those described by Hong et al., Tetrahedron Ltt., **1994,** 35, 6631; or similar to those described in US Patent No. 5,495,054. A protecting group P^2 may be introduced by standard methods, for example by the addition of tert-butydimethylsilylchloride (TBDMS-Cl) and dissolved in a suitable solvent such as dichloromethane.

Brief description of the drawings

Figure 1 shows an x-ray powder diffraction pattern of *N*-{2-[4-((*R*)-2-hydroxy-2-phenylethylamino)phenyl]ethyl}-(*R*)-2-hydroxy-2-(3-formamido-4-hydroxyphenyl) ethylamine monohydrochloride (Compound (Ia) monohydrochloride).

For a better understanding of the invention, the following Examples are given by way of illustration.

LCMS analysis was conducted on a Phenomenex Luna C18(2) column (50 mm x 2.0 mm ID, 3um), eluting with 0.05%v/v trifluoroacetic acid in water (solvent A), and 0.05%v/v trifluoroacetic acid in acetonitrile (solvent B). An elution gradient of 0% solvent B to 95% solvent B over 8 minutes at a flow rate of 1.0 ml/min was used. The mass spectra were recorded on a Micromass Q-ToF spectrometer using electrospray positive mode (ES+ve).

XRPD analysis shown in Figure 1 was performed on a Bruker X-ray powder diffractometer, Model D8 Advance, serial number ROE 2357. The method runs from 2 to 40 degrees 2-Theta with a 0.0145 degree 2-Theta step size and a 1 second collection time at each step.

The differential scanning calorimetry analysis was obtained with a Perkin Elmer instrument model Pyris 1. Samples were weighed into a 50 microlitre aluminium pan, an aluminium lid placed on top of the sample and compressed with a brass rod. An aluminium cover was placed on top of the pan and sealed using a universal press. An empty pan, lid and cover serving as a reference. Samples were equilabrated at 30 °C and heated at 10 °C per minute to a temperature of 300 °C. The instrument was calibrated using indium, tin and lead standards.

Abbreviations

TBDMS-Cl: *tert*-butyldimethylsilyl chloride
DCM: dichloromethane
DMA: *N*,*N*-dimethylacetamide
MEK: 2-Butanone (methylethyl ketone)
NMP: N-methylpyrrolidone
IPA: Isopropylalcohol
IMS: industrial methylated spirit (in the following examples composition of IMS was Ethanol -96%, methanol 4%)

Reference Examples

a) Synthesis of 2-[4-((*R*)-2-hydroxy-2-phenylethylamino)phenyl]ethylamine (2)

To a 1000 mL 3-neck flask was added 10 g (74 mmol) of 2-(4-aminophenyl)ethylamine and 15 mL of 1,3-dimethyl-3,4,5,6-tetrahydro- 2(1*H*)pyrimdinone (DMPU). The reaction flask was fitted with an overhead stirrer, a 125 mL addition funnel and a thermometer. The reaction flask was purged with nitrogen and placed in a cold water bath. The addition funnel was charged with 83 mL (83 mmol) of 1.0 M sodium bis(trimethylsilyl)amide in tetrahydrofuran. The sodium bis(trimethylsilyl)amide solution was added dropwise over 30 min with vigorous stirring. The addition funnel was removed and replaced with a rubber septum. (*R*)-styrene oxide (8.4 mL, 74 mmol) was added dropwise by syringe over 10 minutes. The rate of addition was controlled to maintain a temperature below 35° C. After 1 h, the reaction was quenched by dropwise addition of 88 mL water. The reaction mixture was transferred to a separatory funnel, diluted with 56 mL isopropyl acetate and washed with 84 mL saturated aqueous sodium chloride. The organic layer was washed a second time with a mixture of 84 mL water and 84 mL saturated aqueous sodium chloride

and finally with 84 mL saturated aqueous sodium chloride. The organic layer was concentrated under vacuum. The residue was twice reconcentrated from isopropanol (55 mL portions) and then redissolved in isopropanol (235 mL) and heated to 70°C with stirring. Concentrated hydrochloric acid (13.2 mL, 160 mmol) was added over two minutes. The mixture was allowed to cool to room temperature and stirred for 14 h. The precipitated product was isolated by filtration and washed with isopropanol and isopropyl acetate. The product was dried under vacuum for 3 h and then dissolved in 56 mL water and transferred to a separatory funnel. Isopropyl acetate (56 mL) and 10 N aqueous sodium hydroxide (19 mL, 190 mmol) were added. The separatory funnel was shaken and the phases separated. The organic layer was dried over sodium sulfate and concentrated to afford the product (**2**) as an orange-brown oil (11 g, 44 mmol, 59%). *m/z:* [M + H^+] calcd for $C_{16}H_{20}N_2O$ 257.2; found 257.2.

b) Synthesis of 2-bromo-(*R*)-1-*tert*-butyldimethylsiloxy-1-(3-formamido-4-benzyloxyphenyl)ethane (4)

(*R*)-2-Bromo-1-(3-formamido-4-benzyloxyphenyl)ethanol (intermediate **3**) (9.9 g, 28 mmol) was dissolved in 36 mL dimethylformarnide. Imidazole (2.3 g, 34 mmol) and *t*-butyldimethylsilylchloride (4.7 g, 31 mmol) were added. The solution was stirred under nitrogen atmosphere for 72 h. Additional imidazole (0.39 g, 5.7 mmol) and *t*-butyldimethylsilylchloride (0.64 g, 4.3 mmol) were added and the reaction was stirred for an additional 20 h. The reaction was diluted with a mixture of isopropyl acetate (53 mL) and hexanes (27 mL) and transferred to a separatory funnel. The organic layer was twice washed with a mixture of water (27 mL) and saturated aqueous sodium chloride (27 mL) followed by a final wash with saturated aqueous sodium chloride (27 mL). The organic layer was dried over sodium sulfate. Silica gel (23.6 g) and hexanes (27 mL) were added and the suspension was stirred for 10 minutes. The solids were removed by filtration and the filtrate concentrated under vacuum. The residue was crystallized from hexanes (45 mL) to afford 8.85 g (19 mmol, 68 %) of intermediate **4** as a white solid. *m/z:* [M + H^+] calcd for $C_{22}H_{30}NO_3SiBr$ 464.1, 466.1; found 464.2, 466.4.

c) Synthesis of *N*-{2-[4((*R*)-2-hydroxy-2-phenylethylamino)phenyl]ethyl}(*R*)-2-*tert*-butyldimethylsiloxy-2-(3-formamido-4- benzyloxyphenyl)ethylamine (5)

Intermediate **4** (5.0 g, 11 mmol), intermediate **2** (3.5 g, 14 mmol), and dimethylsulfoxide (10 mL) were combined in a 100 mL round bottom flask and stirred to form a homogeneous solution. Potassium carbonate (6.0 g, 43 mmol) and sodium iodide (1.7 g, 11 mmol) were added and the reaction mixture was heated to 140°C. The reaction

mixture was maintained at 140°C for 10 min, then cooled to room temperature and diluted with water (24 mL) and isopropyl acetate (28 mL). The reaction was stirred until all solids dissolved and then transferred to a separatory funnel. The organic layer was washed with water (17 mL) followed by acetate buffer (5% v/v acetic acid, 12% *w/v* sodium acetate trihydrate in water, 18 ml) followed by sodium bicarbonate solution (5% *w/v* in water, 17 mL) followed by saturated aqueous sodium chloride (17 mL). The organic layer was dried over sodium sulfate and concentrated to afford intermediate 5 as a brown gelatinous solid (7.0g, 11 mmol, >99%). *m/z:* [M + H^+] calcd for $C_{38}H_{49}N_3O_4Si$ 640.4; found 640.6.

d) Synthesis of *N*-{2-[4-((*R*)-2-hydroxy-2-phenylethylamino)phenyl]ethyl}-(*R*)-2-hydroxy-2-(3-formamido-4-benzyloxyphenyl)ethylamine (6)

Intermediate **5** (5.2 g, 8.1 mmol) was dissolved in tetrahydrofuran (26 mL) and triethylamine trihydrofluoride (1.4 mL, 8.6 mmol) was added. The solution was stirred for 20 h. The reaction was quenched by addition of water (7.6 mL) followed by 10.0 N sodium hydroxide (3.8 mL, 38 mmol). After 3 min, the reaction was diluted with isopropyl acetate (20 mL) and transferred to a separatory funnel. The mixture was shaken and the biphasic mixture was filtered through celite to remove undissolved solids. The filtrate was returned to a separatory funnel and the phases were separated. The organic layer was washed with a mixture of 9 mL water and 9 mL saturated aqueous sodium chloride followed by 15 mL of saturated aqueous sodium chloride. The organic layer was dried over sodium sulfate and concentrated to afford the product **6** as a brown gelatinous solid (4.2 g, 8.0 mmol, 99%). *m/z:* [M + H^+] calcd for $C_{32}H_{35}N_3O_4$ 526.3; found 526.4.

e) Synthesis of *N*-{2-[4-((*R*)-2-hydroxy-2-phenylethylamino)phenyl]ethyl}-(*R*)-2-hydroxy-2-(3-formamido-4-hydroxphenyl)ethylamine (1)

Intermediate **6** (2.5 g, 4.8 mmol) was dissolved in 8.0 mL of ethanol and treated with activated charcoal, Darco G-60 (1.25 g). The suspension was stirred at 50°C for 20 min and then filtered to remove the Darco. To the filtrate was added 10% palladium on activated carbon (250 mg) and the suspension placed on a Parr shaker. The reaction was shaken for 10 h under 30 psi hydrogen gas. The reaction was filtered through celite and concentrated under vacuum to afford compound **1** as a brown gelatinous solid (1.9 g, 4.3 mmol, 91%). ^{1}HNMR (300 MHz, DMSO-d_6) δ 2.40-2.68 (m, 6H), 2.92-3.18 (m, 2H), 4.35-4.45 (m, 1H), 4.60-4.69 (m, 1H), 5.22-5.30 (m, 1H), 6.82 (s, 1H), 6.85 (s, 1H), 6.68-6.86 (m, 4H), 7.12-7.36 (m, 5H), 7.95 (d, 1H, *J*= 1.4 Hz), 8.19 (s, 1H), 9.49 (br s, 1H). *m/z:* [M + H^+] calcd for $C_{25}H_{29}N_3O_4$ 436.2; found 436.4.

f) Crystallization of *N*-{2-[4-((*R*)-2-hydroxy-2-phenylethylamino)phenyl]ethyl}-(*R*)-2-hydroxy-2-(3-formamido-4- hydroxyphenyl)ethylamine monohydrochloride

In a 500 mL round bottom flask, compound 1 (5.2 g, 11.9 mmol) was dissolved in 187.9 mL isopropyl alcohol with stirring at 40°C. Complete dissolution was achieved within 10 minutes. The flask was then charged with a solution containing 1.0 N HCl (11.3 mL, 11.3 mmol, 0.95 eq.) and H_2O (29.6 mL). The solution was stirred and the product crystallized over several hours. After 6h, the crystals were isolated by filtration and washed with 15 mL ice-cold 15% water in isopropyl alcohol solution followed by 15 mL of isopropyl alcohol. The crystals were dried under house vacuum for 12-16 h to afford the monohydrochloride salt of compound 1 (3.92 g, 8.3 mmol, 70% yield, 98.89% purity by HPLC) as a white crystalline solid. Water content 0.2 %, ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 10.13 (s, 1H), 9.62 (m, 1H), 8.93 (br s, 1H), 8.66 (br s, 1H), 8.27 (d, 1H, J=1.92), 8.13 (d, 1H, J=1.65), 7.21-7.40 (m, 5H), 6.86-6.94 (m, 4H), 6.57 (d, 2H, J=8.52), 6.05 (d, 1H, J=3.57), 5.45-5.55 (m, 2H), 4.80 (m, 1H), 4.70 (m, 1H), 2.70-3.24 (m, 8H). Elemental analysis (wt %) calcd for $C_{25}H_{29}N_3O_4$.HCl: C, 63.62; H, 6.41; N, 8.90; Cl, 7.51. found: C, 63.47; H, 6.54; N, 8.81; Cl, 7.78.

Example 1

i) 2-Bromo-(*R*)-1-*tert*-butyldimethylsiloxy-1-(3-formamido-4-benzyloxyphenyl)ethane

A solution of TBDMS-Cl (40.1 g, 0.26 mol) in DCM (37.5 mL) was added to a slurry of imidazole (21.86 g, 0.32 mol) and (*R*)-2-bromo-1-(3-formamido-4-benzyloxyphenyl)ethanol (74.54 g, 0.21 mol) in DCM (260 mL) over 8 minutes. The mixture was stirred for 22 hours. The reaction was quenched with water (190 mL) and the aqueous layer was extracted with DCM (37.5 mL). The combined DCM layers were distilled at atmospheric pressure to a volume of ca. 110 mL. On cooling, spontaneous crystallisation occurred. Isooctane (750 mL) was added dropwise over 20 minutes. The slurry was cooled to 0 °C and the solids were collected by filtration then washed with 9:1 v/v isooctane:DCM (3 x 75 mL) and dried *in vacuo* to give the *title compound* as a colourless solid (89.65 g, 90%th). ^{1}H NMR in accord with structure (400 MHz, $CDCl_3$) δ(ppm): -0.06 (3H) s; 0.11(3H) s; *0.12 (3H) s; *0.89 (9H) s; 0.90 (9H) s; *3.38-3.49 (2H) m; 4.78-4.87 (1H) m; *5.09 (2H) s; 5.10 (2H) s; 6.96 (1H) d, J=8.6Hz; *7.06 (1H) d of d, J=8.3, 2.0Hz; 7.11 (1H) d of d, J =8.3Hz, 2.0Hz; 7.25-7.27 (1H) m; 7.36-7.45 (5H) m; *7.70 (1H) d, J=11.0Hz; 7.79 (1H) s; 8.38 (1H) d, J=2.0Hz; 8.42 (1H) d, J=1.5Hz; *8.76 (1H) d, J=11.8Hz.

* Peaks are due to ca 25M% of the minor rotamer.

ii) *N*-{2-[4-((*R*)-2-hydroxy-2-phenylethylamino)phenyl]ethyl}-(*R*)-2-hydroxy-2-(3-formamido-4-benzyloxyphenyl) ethylamine monohydrochloride

2-[4-((*R*)-2-Hydroxy-2-phenylethylamino) phenyl]ethylamine (19.8 g, 60 mmol) was dissolved in water (80 mL). Isopropyl acetate (100 mL) was added with stirring. 32% w/v aqueous sodium hydroxide solution (17.2 mL) was added with stirring over 8 minutes. The organic layer was washed with water (100 mL) then distilled at atmospheric pressure to a volume of ca. 70 mL.

To this solution was added DMA (50 mL) followed by 2-bromo-(*R*)-1-*tert*-butyldimethylsiloxy-1-(3-formamido-4-benzyloxyphenyl)ethane (20 g, 43 mmol) and potassium carbonate (7.44 g, 54 mmol). The mixture was heated at 90 °C (oil bath temperature) for 17 hours then cooled to 50 °C. Water (150 mL) was added and the mixture was cooled further to room temperature. MEK (150 mL) was added and the layers were separated. The organic layer was washed with 17:40:340 v/w/v acetic acid:sodium acetate:water (100 mL) followed by 29% w/v aqueous sodium chloride solution (100 mL). The organic layer was diluted with MEK (50 mL) and then distilled at atmospheric pressure to a volume of ca 150 mL. More MEK (50 mL) was added followed by a solution of cesium fluoride (8.1 g, 51.6 mmol) in methanol (100 mL). The mixture was heated at 37 °C for 7.5 hours then cooled to 30 °C. The reaction was quenched with 44% w/v aqueous potassium carbonate solution (100 mL) and water (20 mL) was added. The organic layer was washed with 29% w/v aqueous sodium chloride solution (100 mL) then treated with acetic acid (3.7 mL, 64.6 mmol). The mixture was washed with 29% w/v aqueous sodium chloride solution (100 mL) followed by 6% w/v aqueous sodium chloride solution (3 x 100 mL).

The solution was diluted with MEK (100 mL) then distilled to a volume of ca 120 mL. MEK (80 mL) was added and the mixture was seeded (seeds may be obtained as described in Example 2). The mixture was distilled again to a volume of ca. 140 mL. More MEK (60 mL) was added and the mixture was cooled to room temperature. The solids were collected by filtration, washed with MEK (3 x 20 mL) and dried *in vacuo* to give the *title compound* as a colourless solid (18.64 g, 77%th). ^{1}H NMR in accord of structure (400 MHz, DMSO-d_6) δ(ppm): 2.70-2.89 (2H) m; 2.95 (1H) m; 3.01-3.14 (4H) m; 3.14-3.23 (1H) m; 4.71 (1H) m; 4.81 (1H) m; *5.17 (1H) s; 5.23 (1H) s; 5.46 (1H) d, J=4.4Hz; 5.50 (1H) m;

6.10 (1H) d, J=3.2Hz; 6.59 (2H) d, J=8.3Hz; 6.94 (2H) d, J=8.3Hz; 7.03 (1H) d of d, J=8.6, 2.0Hz; 7.12 (1H) d, J=8.6Hz; 7.25 (1H) m; 7.30-7.36 (3H) m; 7.36-7.42 (4H) m; 7.50 (2H) d, J=7.3Hz; 8.26 (1H) d, J=2.0Hz; 8.35 (1H) d, J=1.7Hz; *8.54(1H) d, J=11.0Hz; 8.63 (2H) broad res; *9.64 (1H) m; 9.67 (1H) s.

* Peaks are due to ca 11.5M% of the minor rotamer.

iii) *N*-{2-[4-((*R*)-2-Hydroxy-2-phenylethylamino)phenyl]ethyl}-(*R*)-2-hydroxy-2-(3-formamido-4-hydroxyphenyl) ethylamine monohydrochloride

A mixture of *N*-{2-[4-*((R)*-2-hydroxy-2-phenylethylamino)phenyl]ethyl}-(*R*)-2-hydroxy-2-(3-formamido-4-benzyloxyphenyl) ethylamine monohydrochloride (40g) and 5% Pd/C catalyst (Englehard 167, 50% wet with water) (200mg) in NMP (120ml) was stirred under hydrogen at 22±2°C. The mixture was filtered (Whatman GF/F filter) when analysis, by hplc (detection at 220nm), of the reaction mixture showed <0.5% (by area) of the starting material (product of Ex 1ii). The filter cake was washed with a mixture of NMP and IPA (1:1) (80ml).

The combined filtrates were stirred and heated to 69±3°C. Water (10ml) was added. IPA (100ml) was added at a rate that maintained the temperature at 69±3°C. Seed crystals (0.8g) were added. IPA (50ml) was added over 15minutes. The resulting mixture was stirred for about 0.75h. IPA (250ml) was then added over about 2.5h. The resulting slurry was allowed to cool slowly to 20±3°C and stirred at this temperature for ca 16h.

The resulting slurry was cooled to 3±3°C and stirred at this temperature for 4h. The slurry was filtered and the collected solid was washed successively with IPA/water (10:1) (80ml) and IPA (160ml). The solid was dried under vacuum at ca 50°C to give the *title compound* as a white solid (29.7g).

Yield: 88%th, 74%w/w

NMR: δ(ppm): 2.73-2.89 (2H) m; 2.95 (1H) m; 3.01-3.14 (4H) m; 3.15-3.24 (1H) m; 4.72 (1H) m; 4.82 (1H) m; 5.46 (1H) d, J = 4.7Hz; 5.48 (1H) m; 6.03 (1H) d, J=3.4Hz; 6.59 (2H) d, J=8.6Hz; 6.89 (1H) d, J=8.1Hz; 6.91-6.98 (3H) m; *7.01 (1H) d, J=8.6Hz; *7.14 (1H) s; 7.25 (1H) t, J=7.3Hz; 7.33 (2H) t, J=7.3, 7.6Hz; 7.39 (2H)

d, J=7.6Hz; 8.13 (1H) d, J=1.5Hz; 8.29 (1H) d, J=1.7Hz; *8.53 (1H) d, J=11.0Hz; 8.57-9.08 (2H) broad res; *9.36 (1H) d, J=11.0Hz; 9.60 (1H) s; *9.92 (1H) s; 10.10 (1H) s.

* Peaks are due to ca 11M% of the minor rotamer.

iv) Recrystallisation of *N*-{2-[4-((*R*)-2-Hydroxy-2-phenylethylamino)phenyl]ethyl}-(*R*)-2-hydroxy-2-(3-formamido-4-hydroxyphenyl) ethylamine monohydrochloride

The title mononydrochloride (5g) was suspended in aqueous industrial methylated spirit (IMS) (2:1 IMS:water, 72.5ml) in a 100ml round bottomed flask. The mixture was warmed to 78°C to give a clear solution. This was filtered, washed through with aqueous IMS (2:1 IMS:water, 2.5ml) and the liquor rewarmed to 78°C to re-dissolve the solid that precipitated during the filtration. The temperature was adjusted to 65°C and seeded with monohydrochloride (10mg). The mixture was held at 60-65°C for 2 hours and then cooled to 20-25°C and stirred at that temperature for 14 hours. The suspension was chilled to 0-5°C and held at that temperature for 3 hours. The product was collected via filtration, and washed with aqueous IMS (2:1 IMS: water, 2 X 7.5ml) and then IMS (3 X 7.5ml) to give the *title compound* as a white solid, which was dried at 50°C under vacuum overnight.

Expected yield: 80%th, 80%w/w

The XRPD pattern of this product is shown in Figure 1.

The differential scanning calorimetry trace for this product shows an absence of discernable endothermic features below about 125°C, with minor endothermic events having onsets at about 133 °C, about 151 °C and at about 170 °C.

Example 2

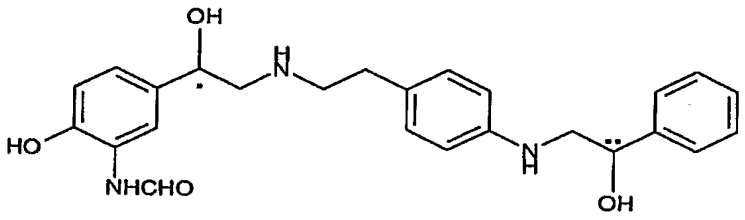
***N*-{2-[4-((*R*)-2-hydroxy-2-phenylethylamino)phenyl]ethyl}-(*R*)-2-hydroxy-2-(3-formamido-4-benzyloxyphenyl) ethylamine monohydrochloride**

N-{2-[4-((*R*)-2-hydroxy-2-phenylethylamino)phenyl]ethyl}-(*R*)-2-hydroxy-2-(3-formamido-4-benzyloxyphenyl) ethylamine (96.1 mg, 0.18 mmol) was dissolved in 2-propanol (2.2 mL)

with warming. A solution of hydrochloric acid in dioxane (4 M, 45 μL, 0.18 mmol) was added. At the end of the addition the majority of material was present as a gum which was stirred at room temperature overnight. The solids were collected by filtration, washed with 2-propanol (3 x 1 mL) and dried by suction on the filter to give the *title compound* as a colourless solid (69.5 mg, 69%). ^{1}H NMR in accord with structure (400 MHz, DMSO-d_6,).

CLAIMS

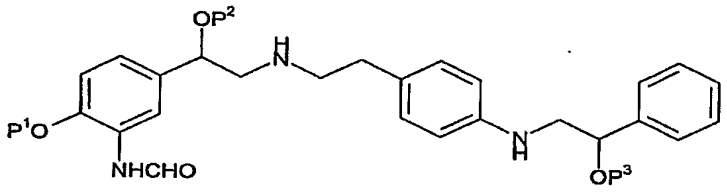
1. A process for preparing a monohydrochloride salt of compound (I)



(I)

wherein *C and **C denote asymmetric carbon atoms,
which process comprises the steps of:

a) contacting a compound of formula (II):



(II)

wherein P^1 represents a hydroxyl protecting group, and P^2 and P^3 each independently represents hydrogen or a protecting group;

with a weak acid, to effect selective protonation;

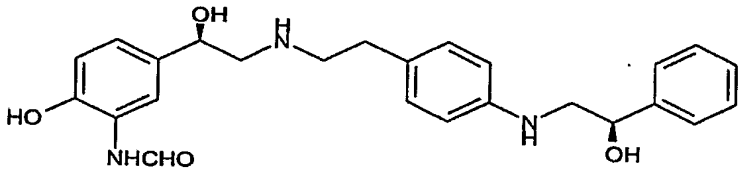
b) contacting the product of (a) with a source of chloride ions, to effect anion exchange;

c) deprotection to remove P^1, and where necessary P^2 and P^3;

d) isolation of compound (I) as the monohydrochloride; and optionally

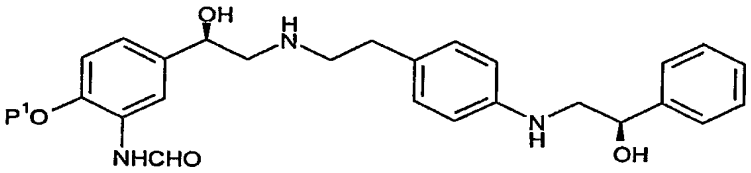
e) crystallisation or recrystallisation of compound (I).

2. A process according to claim 1, wherein the compound of formula (I) is the compound (Ia):



(Ia)

and the compound of formula (II) is the compound (IIa):



(IIa)

wherein P^1 is as defined in claim 1.

3. A process according to claim 1 or claim 2 wherein the weak acid is acetic acid.

4. A process according to any of claims 1 to 3 wherein the group P^1 represents benzyl.

5. A process according to any of claims 1 to 4 wherein the source of chloride ions is sodium chloride.

6. A process according to any of claims 1 to 5 for the preparation of a crystalline monohydrochloride salt of the compound of formula (Ia).

7. A process according to claim 6 wherein the product of said process is characterised by an x-ray powder diffraction pattern in which the peak positions are substantially in accordance with the peak positions of the pattern shown in Fig. 1.

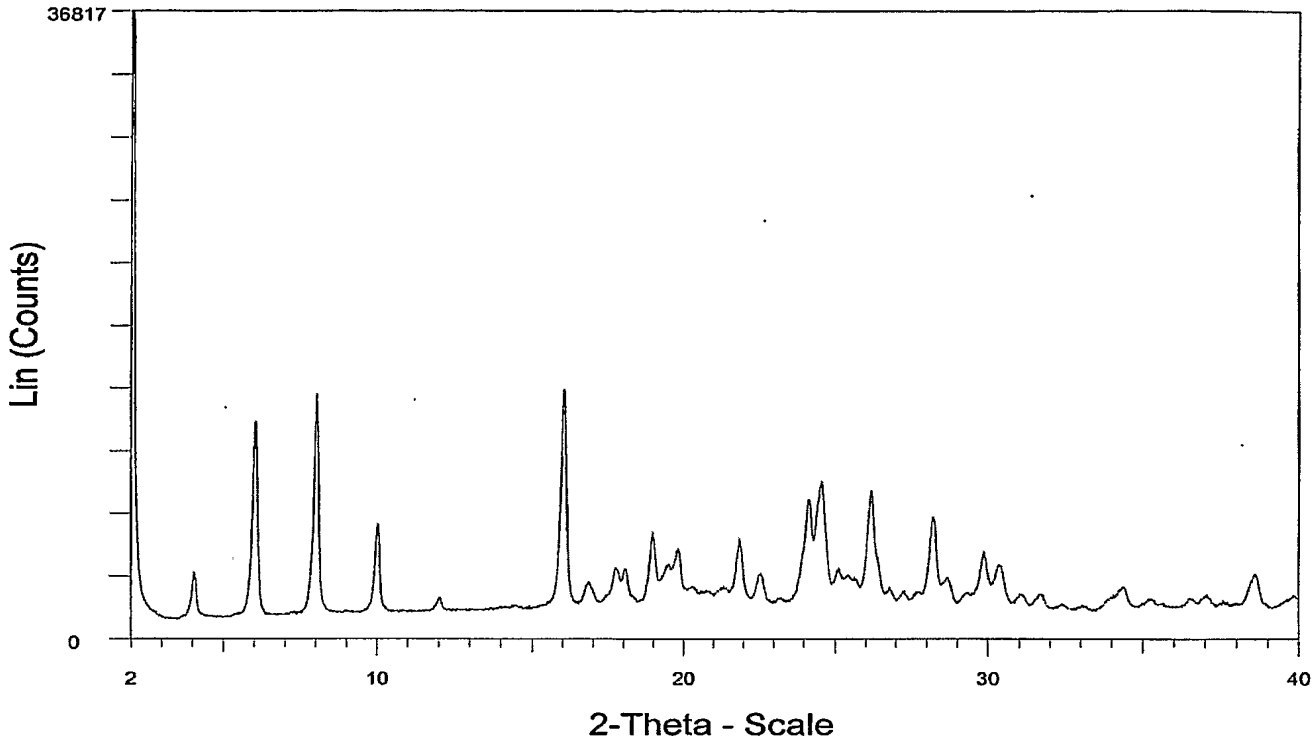
8. Crystalline (Ia) monohydrochloride which is characterised by a differential scanning calorimetry trace which shows an absence of discernable endothermic features below about 125°C.

9. Crystalline (Ia) monohydrochloride which is characterised by a differential scanning calorimetry trace which shows an absence of discernable endothermic features below about 125°C, and an onset of significant endothermic heat flow at about 229°C.

10. Crystalline (Ia) monohydrochloride which is characterised by a differential scanning calorimetry trace which shows an absence of discernable endothermic features below about 125°C, two or more minor endothermic events between about 130°C and about 180°C and an onset of significant endothermic heat flow at about 229°C.

11. Crystalline (Ia) monohydrochloride according to claim 10 wherein said minor endothermic events occur at about 133°C, at about 151°C and at about 170°C.

Figure 1



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